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TRANSMITTAL LETTER Applicant(s): Molly F. Kulesz-Martin			Attorney Docket No: RPP:135D US
Serial No: 08/644,289	Filing Date: May 10, 1996	Examiner: Y. Eyler	Art Unit: 1642
Invention: p53as PROTEIN AND ANTIBODY THEREFOR			

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:

#24 8/7/00 T. Gray

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Respectfully submitted,

Dated: July 28, 2000

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Molly F. Kulesz-Martin

Art Unit: 1642

#24 8/7/00 T. Gray

Serial No: 08/644,289

Filed: May 10,1996

I certify that this **APPEAL BRIEF** is being deposited on **July 28, 2000** with the U.S. Postal Service as first class mail addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231

Examiner: Y. Eyler

For: p53as PROTEIN AND ANTIBODY THEREFOR

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APPEAL BRIEF
(37 CFR 1.192)

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Sir:

Applicants respectfully appeal the decision of the Examiner finally rejecting Claims 1, 3-6, and 8-19 as set forth in his Office Action dated February 1, 2000. A Notice of Appeal was timely filed by the Applicants on June 5, 2000.

Real Parties in Interest

The real party in interest is Health Research, Inc., Assignee of the above application by assignment recorded in the Patent and Trademark Office at Reel 8019, Frame 0490.

Related Appeals and Interferences

There are no related appeals or interferences.

Status of Claims

The application originally contained 15 claims. Claims 2 and 7 have been cancelled and 12-14 have been withdrawn by the Examiner as being drawn to a non-elected invention. Claims 16-19 have been added by amendment. Claims 1, 5 and 15-19 have been amended. Claims 1, 3, 8-11 and 15-19 are pending on Appeal.

Status of Amendments

Claims 1, 5, and 15-19 have been amended. No amendments have been offered which have not been entered.

Summary of the Invention

The invention is a plasmid or viral vector containing a cDNA sequence which encodes a protein designated p53as. The p53as is functionally equivalent in growth regulation to active wildtype p53, and the p53 and p53as are sequentially the same up to the final 50 carboxy terminal amino acids of p53. The p53as is, however, different than p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus and so as to provide an epitope within said p53as which gives rise to an antibody which is specific only for p53as protein.

Issues Presented for Review

1. Whether claims 1, 3-6, and 8-11, and 15-19 are patentable under 35 USC 112 second paragraph;

2. Whether claims 1, 3-6, 8-11, and 16-19 are patentable under 35 U.S.C. 112 first paragraph;

3. Whether claims 1, 3, 4 and 17 are patentable under 35 U.S.C. 103(a) over Han et al. (Nuc. Acids Res. 20:1979-1981, 1992) in view of Sambrook et al. (Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1989); and

4. Whether Claims 5, 6, 8-11 and 18 are patentable under 35 U.S.C. 103(a) over Han et al. (Nuc. Acids Res. 20:1979-1981, 1992) in view of Lee et al. (EP 529.160).

The rejections under 35 U.S.C. 102 over Wolf et al. or Arai et al. were withdrawn in the advisory action.

The rejections under 35 U.S.C. 103 over Wolf et al. or Arai et al. in view of Lee were withdrawn in the advisory action.

Grouping of Claims

The claims do not stand or fall together. The subclaims further restrict the independent claims to particular species thus providing further arugment against 35USC112 rejections. Furthermore, the specific embodiments in the subclaims are specifically not described in the cited art. Additionally, all claims are not subject to the same rejections.

Argument

In the last official action, the Examiner rejected claims 1, 3-6, and 8-11, 15, 17 and 18 under 35 U.S.C. 112.

The Examiner argues that Harris et al. teaches that the "activity" of p53 is dependent upon many factors and thus the term "active" is unclear. Harris et al. clearly understands what is

meant by "active". Harris et al's question isn't concerned with the meaning of the word "active' but with what causes p53 to be active or not. In the cited reference to describe p53 function, Harris uses the words "inactivated", "inactivation", "transactivate", "transactivation", "transactivator", "inactive", "inactivation", "activate", and "activity", collectively, at least 23 times. Harris says right in the abstract "p53 is functionally ***inactivated*** by structural mutations, interaction with viral products, and endogenous cellular mechanisms in the majority of human cancers." (emphasis added). There is apparently no confusion by Harris as to what "inactivated" means and Harris is clearly a person skilled in the art. It does not seem appropriate that the Examiner should second guess the clearly skilled person in the art and imply that Harris doesn't know the meaning of the words he uses. Harris et al's concerns with mode of activation don't apply to p53as as presently claimed since the claimed p53as is always active due to the absence of the regulatory domain present in p53. **There is clearly no ambiguity in the use of the word "active" in the claims.**

The present invention is not difficult to understand in view of the specification and claims. One skilled in the art already knows a myriad of effects of p53. One skilled in the art already knows that p53 has growth regulating properties discussed in literally hundreds of documents. One skilled in the art already knows that p53 has a terminal negative regulatory domain that can turn off many, if not all, of the growth regulating properties of p53 under certain conditions. One skilled in the art already knows that when the negative regulatory domain is removed, the growth regulating properties of p53 can no longer be turned off.

The Examiner is referred to the references cited in the information disclosure statement as examples of such known information and is especially referred to Hupp et al cited by the Applicant that shows that removal of the C-terminal regulatory domain permanently activates p53. ***This paper was accepted for publication in the prestigious technical journal "Cell" in 1992 after peer review. Neither the reviewers nor the magazine had any difficulty understanding the meaning of "active" p53 or the its" function".*** **It is asserted that since those skilled in the art understand the meaning of these terms, any objection by the Examiner to their use should be dropped and the rejection should be reversed**.

Claims 16 and 19 have been rejected under 35 U.S.C. 112 as being indefinite because there is no definition "what constitutes a portion." With due respect to the Examiner, there are only 18 amino acids in the peptide in question. It is a relatively simple matter to truncate the peptide from either or both ends and test the truncated peptide to determine whether it raises an antibody response. With only 18 starting amino acids, there would seem to be no more than about ten possibilities for a "portion" that will raise an antibody response. Again, the Examiner seems to be making the invention more complicated than it really is. The "portion" would be expected to be linear since large amounts of folding could hardly be expected with 17 amino acids or less and in any case if the truncated sequence did naturally fold, the mode of operation need not be claimed or even described so long as an antibody response occurs. The inventors should not be required to restrict their invention to exclude reasonable modifications that are well within the purview of the skilled artisan. These claims are not indefinite.

The rejection should be reversed.

Claims 1, 3-6, 8-11, 17 and 18 have been rejected under 35 U.S.C. 112 as containing subject matter not sufficiently described in the specification. This rejection should be reversed.

The Examiner should again be reminded that a patent specification is not intended to be a textbook including all information known and readily available to a skilled person. If such were not the case, every patent specification would be thousands of pages long rehashing known material ad nausem and hiding the nature of the improvement of the invention within unnecessarily included information.

The Examiner is making the invention much more complicated than it is. The invention is easy to understand and can be practiced to the extent of the breadth of the claims by one of even meager skill in the art in view of the teachings of the specification.

As previously discussed, one skilled in the art already knows a myriad of effects of p53. One skilled in the art already knows that p53 has growth regulating properties discussed in literally hundreds of documents. One skilled in the art already knows that p53 has a terminal negative regulatory domain that can turn off many, if not all, of the growth regulating properties of p53 under certain conditions. One skilled in the art already knows that when the negative regulatory domain is removed, the growth regulating properties of p53 can no longer be turned off.

The Examiner is again referred to the references cited in the information disclosure statement as examples of such known information and is especially referred to Hupp et al cited by the Applicant that shows that removal of the C-terminal regulatory domain permanently activates p53.

The present invention points out that in view of the above, one would further expect that the growth regulating properties of p53 also could no longer be turned off if the terminal regulatory domain of p53 were modified or substituted to interfere with its function and demonstrated that to be the case by the discovery of terminally modified p53 that cannot be turned off (p53as) and that has a terminal sequence that raises a unique antibody.

One skilled in the art knows the sequence of p53. One skilled in the art knows many epitopes that can raise unique antibodies. One skilled in the art already knows how to truncate p53 to remove the negative regulatory domain and one skilled in the art already knows how to connect different sequences. **Attaching unique epitopes to proteins and peptides is now an essentially cookbook procedure performed routinely by laboratory technicians , e.g. in ELISA analysis and for the purpose of tags.**

Therefore, in view of the above discovery by the inventor of terminally modified p53 that cannot be turned off (p53as) having a terminal sequence that raises a unique antibody, the inventor concluded that p53 could be easily truncated to remove the negative regulatory domain and a large number of different terminal sequences could be substituted that raise unique antibodies. Once the inventor made this previously unobvious suggestion, anybody skilled in the art could practice the invention. The probability that such a new terminal sequence would also have a negative regulatory domain effect upon p53 is infinitesimal. In view of her discovery and teaching it becomes clear that known methodologies may be combined to practice the invention and that it would be surprising if the p53as having unique terminal

sequences did not function as active p53 and it would be further surprising if the p53as having unique terminal sequences did not raise the expected unique antibodies.

Further, if there are any p53 terminal sequences, as above described, that do not function as active p53 and that do not produce unique antibody, such could easily be detected in view of existing knowledge.

The Examiner states that the "specification does not contemplate the addition of exogenous, non-p53, sequences, such as his-tag epitopes." The Examiner's statement is not correct. For example, page 3, line 6 of the specification says, "To obtain a p53as the terminal amino acids of p53 are preferably modified, i.e. there is at least some substitution, as opposed to simple truncation." **This statement in no way restricts the substitution to p53 sequences.**

Page 2, last paragraph of the specification says "It is to be understood that p53as may be of natural or **synthetic** form, provided that, at a minimum, **terminal amino acids differ** from the 50 terminal amino acids of p53 so that the modified products will act the same as active p53 protein and is functionally equivalent to mouse p53as protein" (emphasis added). **This statement clearly contemplates non-p53 sequences at the terminal end.**

The Examiner apparently continues to be moved by the fact that usually substitution within a protein sequence to obtain similar function is complex. ***The Examiner would normally be correct but is not correct here.*** The functional sequence in p53 and p53as have been identified, are the same and are not being changed. ***Only the terminal regulatory domain is being affected by the changes to obtain the claimed p53as.*** The total elimination of the

regulatory domain in the known art while retaining p53 activity is dispositive of whether or not function may be retained while modifying that domain.

The teaching in the specification with respect to the specific p53as is clearly an example of terminally modified p53 having a unique epitope. The teaching is not limiting but an example.

It is thus clearly taught in the specification that modification of the terminal amino acids of p53 can be used to eliminate the regulatory domain. Nothing further is required to enable one skilled in the art to do it. The advantages of a unique C terminus epitope are also clearly taught. Again, at the present state of the art, any genetic engineering lab technician could add such a unique epitope to the C terminus.

A patent application is not supposed to be a textbook in well understood procedures. The teachings have been made of how to eliminate the negative regulatory domain of p53 by removing or altering the carboxy terminal sequence. Once this teaching is made, one of even menial skill in the art can do it. Further, the desirability of incorporating a unique epitope is taught in the specification. Again, once this teaching is made, one of even menial skill in the art can do it. It is the concepts, taught in the present application, of eliminating the negative regulatory domain and incorporating a unique epitope which is at the heart of the invention. Once these concepts are taught, one having only minimal skill can practice them since only well known standard procedures are needed. Certainly no undue experimentation is required or necessary and the claims to the invention should not be unfairly restricted to merely a single example of the many possibilities for addition of unique epitopes.

In view of the above and other teachings in the specification, one skilled in the art would clearly know that other epitopes could be substituted in the C terminus. The claims have thus been appropriately limited to the minimum difference between p53 and p53as defined on page 2, last paragraph without addition of new matter.

The rejection should be reversed.

Claims 16 and 19 have been rejected under 35 U.S.C. 112 on the ground that use of "any portion of SEQ. ID NO:1" is not enabled. The rejection should be reversed.

SEQ. ID NO.1 is a short sequence and anybody with even minimal skill in the art would be enabled to easily determine whether a portion of that sequence raised an antibody. Undue experimentation would not be required as the test is practically "cookbook". The rejection should be withdrawn.

The Examiner has rejected claims 1, 3, 4, and 17 under 35 U.S.C. 103 over Han et al in view of Sambrook et al. It is asserted that the rejection is improper and should be reversed.

Han et al is interested in sequencing p53as cDNA and for that purpose only incorporates a p53as cDNA segment into a plasmid. The incorporated segment is only about one-third of a complete p53as cDNA. A whole p53as cDNA is never incorporated into a plasmid and in fact would be counterproductive for Han et al's purposes. Large DNA fragments are difficult and sometimes impossible to sequence thus Han et al actually teaches against incorporating an entire p53as cDNA sequence. Han et al. is interested in sequencing and, except for sequencing, teaches nothing at al concerning the study of function (activity) of either p53 or p53as. The "study" referred to by Han et al. clearly relates to sequencing. There is no suggestion

concerning methods for study of function except for sequencing. For the purposes of Han et al. it would have been counterproductive to include a complete p53as into a vector of any kind since long structures are difficult to sequence and are usually broken into smaller segments for that purpose.

Han et al does not incorporate p53as cDNA or any other functional p53 or p53as into anything.

In the last official action, the Examiner has acknowledged that Han et al does not incorporate p53as into anything but based entirely upon hindsight asserts that because Han et al inserts a p53as segment for sequencing it would be obvious to insert the whole p53as for purposes of function. The Examiner reaches that conclusion just because Han et al says "more precise biochemical and biological characterizations of AS-p53 protein ... appear to be critical in future studies of p53 function...." Attributing the teaching of incorporation of a complete p53as into a plasmid or virus based upon the above quoted statement Han et al. is impermissible hindsight at a minimum because Han et al. gives no reason whatsoever to expect that incorporation of a whole p53as into a plasmid or virus would somehow further the study of function. **The only reason that Han et al. incorporated a p53as segment was for sequencing not function. There is simply no suggestion that incorporation of such a segment might be useful to evaluation function and there is certainly no suggestion that incorporation of a whole p53as could somehow be useful for such a purpose.**

The position of the Examiner is contrary to the teaching of Han et al which is to sequence the segment. In general it is not desirable to try to sequence large segments; thus, following the

teachings of Han et al there is no reason to incorporate the entire p53as. The Examiner's extension of Han et al to the entire p53as is classical hindsight. In the absence of the teaching of the present application, there would simply be no reason to incorporate the entire p53as into a vector of any kind.

Combining Han et al with Sambrook et al accomplishes nothing. It is a giant reach to state that because Sambrook et al generically discloses expressing large amounts of protein with nothing at all suggested concerning p53as, that Han et al somehow suggests incorporating a whole p53as. This is a cleanly impermissible hindsight combination. Further, a generic teaching of expressing a large amount of protein is not equivalent to saying that long sequences can or should be incorporated into plasmids. Large amounts of protein and long sequences are not the same thing or even similar. One has essentially nothing to do with the other.

The rejection should be reversed.

The rejection of Claims 5, 6, 8-11 and 18 over Han et al in view of Lee et al is a similarly flawed hindsight combination.

Han et al does not teach or suggest incorporation of p53as into anything, as previously discussed. Citation of Lee et al. which discloses nothing at all concerning p53as, does not cure this defect. The addition of Lee et al to the other cited references accomplishes nothing. Lee et al is generic and says nothing concerning p53 or p53as. Neither reference suggests incorporating p53as into anything; therefore their combination certainly makes no such suggestion.

The rejection should be reversed.

In summary, none of the references cited by the Examiner in any of the rejections suggest incorporating p53as into anything and certainly not into a plasmid or viral vector. None of the cited references have this critical defect cured by anything disclosed in any of the other cited references.

Conclusion

In view of the foregoing, it is clear that the pending claims are patentable over the cited prior art. Reversal of the Examiner and allowance of all claims are therefore respectfully requested.

Respectfully submitted,

Dated: July 28, 2000

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Appendix

Reprinted below are the claims on appeal:

1. A plasmid containing a cDNA sequence which encodes a protein designated p53as, said p53as being functionally equivalent in growth regulation to active wildtype p53, said p53 and p53as being sequentially the same up to the final 50 carboxy terminal amino acids of p53, said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus and so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as protein only.

3. The plasmid of Claim 1 wherein the p53as naturally occurs in a mammal.

4. The plasmid of Claim 1 wherein the p53as is mouse p53as.

5. A viral vector containing a cDNA sequence which encodes a protein designated p53as, said p53as being functionally equivalent to active wildtype p53, said p53 and p53as being sequentially the same up to the final 50 carboxy terminal amino acids of p53, said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus and so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as protein only.

6. The viral vector of Claim 5 wherein the vector is baculovirus vector.

8. The viral vector of Claim 5 wherein the p53as naturally occurs in a mammal.

9. The viral vector of Claim 6 wherein the p53as naturally occurs in a mammal.

10. The viral vector of Claim 5 wherein the p53as is mouse p53as.

11. The viral vector of Claim 6 wherein the p53as is mouse p53as.

12. An antibody wherein the antibody is directed against at least a portion of human p53 intron 10 sequence encoding SLRPFKALVREKGHRPSHSC.

13. The antibody of Claim 12 wherein the antibody is a polyclonal antibody.

14. The antibody of Claim 12 wherein the antibody is a monoclonal antibody.

15. A plasmid containing a p53as gene sequence encoding the peptide SLRPFKALVREKGHRPSHSC, SEQ. I.D. NO. 1.

16. A plasmid containing a p53as gene sequence encoding a portion of the peptide SLRPFKALVREKGHRPSHSC, SEQ. I.D. NO. 1, which peptide will raise an antibody response.

17. A cell transfected with the plasmid of Claim 1.

18. A cell transfected with the viral vector of Claim 5.

19. A viral vector containing a p53as gene sequence encoding a portion of the peptide SLRPFKALVREKGHRPSHSC, SEQ. I.D. NO. 1, which peptide will raise an antibody response.